



DEPARTMENT OF HEALTH & HUMAN SERVICES

95012d
Public Health Service

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Food and Drug Administration
Detroit District
300 River Place
Suite 5900
Detroit, MI 48207
Telephone: 313-393-8100
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September 2, 2004

WARNING LETTER
2004 - DT - 07

Dr. Martin D. Madaus, Ph.D.
President and CEO
Roche Diagnostic Corporation
9115 Hague Road
Indianapolis, IN 46256-1025

Dear Dr. Madaus:

During an inspection of your establishment located in Indianapolis, IN, on May 11-26, 2004, our Investigator determined that your firm markets Tecan Clinical Workstations in three configurations () and () for use in conjunction with other Roche products for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhea*. The Tecan Clinical Workstations are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.

The inspection was conducted in response to FDA's receipt of a Medical Device Report (MDR) concerning the potential for mismatch of patient identification with sample results in the analysis for *Chlamydia trachomatis* and *Neisseria gonorrhea* infective agents.

The inspection revealed that these devices are adulterated under section 501(f)(1)(B) of the Act, in that they are class III devices under section 513(f) and they are not the subject of approved premarket approval applications under section 515(a) or approved applications for investigational device exemptions under section 520(g). These devices are also misbranded under section 502(o), because a notice or other information respecting them was not provided to the FDA as required by section 510(k). For a product requiring premarket approval before marketing, the notification required by section 510(k) of the Act is deemed to be satisfied when a premarket approval application is pending before the agency. 21 CFR 807.81(b)

The addition of the Tecan Clinical Workstations to devices that have previously been cleared for marketing under section 510(k) of the Act is a significant modification of the cleared devices and, consequently, a 510(k) submission is required before the modified devices may be marketed.

Another inspection of your firm was conducted on June 18-28, 2004 to evaluate the production of your ONLINE TDM Phenytoin diagnostic test kit Lot #

The test kit is a medical device as defined by section 201(h) of the Act because it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.

The above-stated inspections revealed that these devices are adulterated under section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System regulation, as specified in Title 21, Code of Federal Regulations CFR, Part 820 (21 CFR 820). Significant deviations include, but are not limited to, the following:

1. Failure to perform all the elements of design control required under 21 CFR 820.30(b) – (h). Specifically, you failed to document a design development plan, design input requirements, essential design outputs, design review, design verification, a risk analysis, and the procedures for transferring the design into production.
See the 5/26/04 FDA-483 # 1.
2. Failure to establish and maintain a design history file to demonstrate that the design of the devices was developed following an approved plan and the design control requirements, as required by 21 CFR 820.30(j).
See the 5/26/04 FDA-483 # 2.
3. Failure to implement procedures to ensure that all purchased products and services conform to specified requirements, as required by 21 CFR 820.50(a) and (b). Specifically, you failed to follow your procedure for adding suppliers of hardware and software accessories used in the devices to include:
 - a. A record that adequate quality requirements are met.
 - b. A record that the supplier has been sufficiently evaluated.
 - c. A record showing the type and extent of control to be exercised over this contractor has been clearly defined.
 - d. Established purchasing information including specified requirements for the products and services to be received.**See the 5/26/04 FDA-483 # 3.**

4. Failure to include in the Device Master Record (DMR) for the devices a reference to the location of the device and software specifications, as required by 21 CFR 820.181.
See the 5/26/04 FDA-483 # 5.
5. Failure of the Device History Record (DHR) to include the original documentation generated during installation and verification testing of the devices, that is performed at the customer's location, as required by 21 CFR 820.184.
See the 5/26/04 FDA-483 # 6.
6. Failure to establish and maintain an adequate organizational structure to ensure that your medical devices are designed and produced in accordance with the requirements of Part 820, as required by 21 CFR 820.20(b), as demonstrated by the observations made during the June 18-28, 2004, inspection.
See the 6/28/04 FDA-483 # 7.
7. Failure to establish and maintain a Quality System that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of Part 820, as required by 21 CFR 820.5. For example:
 - a) Non-conforming ONLINE TDM Phenytoin diagnostic test kits, lot [] were manufactured, released and distributed by your Quality System.
 - b) The ONLINE TDM Phenytoin diagnostic test kits, lot [] were manufactured by an employee who lacked adequate training to perform the complex mathematical calculations required by the Device Master Record.
 - c) The Device Master Record (DMR) for ONLINE TDM Phenytoin diagnostic test kits, lot [] fails to include a statement of the quantity of the ingredient [] to be added to the batch.
 - d) The Device History Record (DHR) fails to accurately reflect the actual conditions of manufacturing the ONLINE TDM Phenytoin diagnostic test kits, lot []**See the 6/28/04 FDA-483 #1- 5.**
8. Failure to assure that personnel are adequately trained to perform assigned functions, as required by 21 CFR 820.25(b).
See the 6/28/04 FDA-483 # 5.

4. Failure to include in the Device Master Record (DMR) for the devices a reference to the location of the device and software specifications, as required by 21 CFR 820.181.
See the 5/26/04 FDA-483 # 5.
5. Failure of the Device History Record (DHR) to include the original documentation generated during installation and verification testing of the devices, that is performed at the customer's location, as required by 21 CFR 820.184.
See the 5/26/04 FDA-483 # 6.
6. Failure to establish and maintain an adequate organizational structure to ensure that your medical devices are designed and produced in accordance with the requirements of Part 820, as required by 21 CFR 820.20(b), as demonstrated by the observations made during the June 18-28, 2004, inspection.
See the 6/28/04 FDA-483 # 7.
7. Failure to establish and maintain a Quality System that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of Part 820, as required by 21 CFR 820.5. For example:
 - a) Non-conforming ONLINE TDM Phenytoin diagnostic test kits, lot [] were manufactured, released and distributed by your Quality System.
 - b) The ONLINE TDM Phenytoin diagnostic test kits, lot [] were manufactured by an employee who lacked adequate training to perform the complex mathematical calculations required by the Device Master Record.
 - c) The Device Master Record (DMR) for ONLINE TDM Phenytoin diagnostic test kits, lot [] fails to include a statement of the quantity of the ingredient [] to be added to the batch.
 - d) The Device History Record (DHR) fails to accurately reflect the actual conditions of manufacturing the ONLINE TDM Phenytoin diagnostic test kits, lot []**See the 6/28/04 FDA-483 #1- 5.**
8. Failure to assure that personnel are adequately trained to perform assigned functions, as required by 21 CFR 820.25(b).
See the 6/28/04 FDA-483 # 5.

9. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications, as required by 21 CFR 820.70(a). **See the 6/28/04 FDA-483 # 1.**
10. Failure to have in-process acceptance activities to ensure that specified requirements for the in-process BULK PHENYTION HAPTEN/CONJ RGT, Lot [], were met, as required by 21 CFR 820.80(c).
See the 6/28/04 FDA-483 # 3.
11. Failure of the Device History Records (DHR) to include or refer to the location of in-process acceptance records to demonstrate that the in-process BULK PHENYTION HAPTEN/CONJ RGT, Lot [] was manufactured according to the Device Master Record and the requirements of 21 CFR Part 820, as required by 21 CFR 820.184(d).
See the 6/28/04 FDA-483 # 4.0
12. Failure of the Device Master Record (DMR) for the in-process BULK PHENYTION HAPTEN/CONJ RGT, Lot [] to include or refer to the location of all production and process specifications, as required by 21 CFR 820.181(b).
See the 6/28/04 FDA-483 # 2.
13. The Corrective and Preventive Action (CAPA) process initiated on 7/18/03 did not meet the requirements of 21 CFR 820.100(a) and, therefore, was not adequate to fully address and resolve the impact of the calculation error that occurred on 5/30/03 during the production of in-process BULK PHENYTION HAPTEN/CONJ RGT, Lot [] after the error was discovered during the checker's review process on 7/17/03.
See the 6/28/04 FDA-483 #6, example #2.

June 17, 2004 Response Letter

We acknowledge your June 17, 2004 letter responding to the FDA-483 issued at the conclusion of the May 11-26, 2004, inspection and we support your steps to establish a US Quality Review Board with the responsibility to assess all aspects of Roche Diagnostics' quality policies, processes, and systems, and for implementing appropriate changes to improve the effectiveness of these systems. We understand that time frames for completion of the assessment of the immediate problems remain indefinite but that a detailed timeline will be provided in future monthly updates. Our comments to the specific responses are as follows.

FDA-483 # 1 and 2

Regarding design of the analyzer systems line of devices, your response to observations 1 and 2 does not definitely commit to performing all the design control and design history file requirements of 21 CFR 820.30.

FDA-483 # 3

Regarding the supplier qualification process, your response appears to be an acceptable solution to the failure to correctly classify the specific suppliers noted on the FDA-483 and perform a retrospective review of all suppliers.

FDA-483 # 4

Regarding the need to correct and prevent recurrence of nonconforming product and other quality problems, we accept your explanation that the previously established corrective action in March 2004 post-dates the timing of the causative events to the problems with the analyzer systems devices subject to the May 2004 inspection and this warning letter.

FDA-483 # 5 and 6

Regarding the deficiencies in the device master and device history records for analyzer systems devices, your response indicates that a more specific corrective action will depend upon the results of your US Quality Review Board assessment that will be provided in more detail in future monthly updates.

July 19, 2004 Response Letter

We acknowledge the July 19, 2004 letter of Mr. Kepten D. Carmichael, Director Regulatory Compliance, responding to the FDA-483 issued at the conclusion of the June 18-28, 2004 inspection. Our comments concerning those responses are as follows.

FDA-483 #1, 3, & 4

The responses to FDA-483 observations 1, 3 and 4 do not appear to address the **in-process acceptance activities** required by 21 CFR 820.80(c) that are designed to ensure production will not continue beyond specific critical steps until the intermediate product is deemed acceptable. Rather, the described corrections appear to implement tighter checking and auditing of the batch record after production is complete, as well as, a new policy of immediate batch rejection in the event that similar calculation errors are discovered.

FDA-483 #2

The response to FDA-483 observation 2 (once implemented on 8/31/04) is an acceptable response to the specific failure to include in the Device Master Record a statement of the quantity of the ingredient [] to be added to the batch.

We recommend that you perform a thorough review of this and all other Device Master Records (DMR's) and the Device History Records generated to implement the DMR in order to simplify the steps used to determine the exact quantities of ingredients required in each batch. We also recommend that you minimize the need for mathematical calculations by the production operators. These changes should eliminate errors as well as the numerous cross-over corrections we noted in the single Device History Record reviewed during this inspection.

FDA-483 #5 and 6

We concur with the FDA investigator's "corrected and verified" annotation of these two observations on the FDA-483 at the conclusion of the inspection. You should ensure that the strengthened CAPA procedure will be fully implemented and enforced at the completion of significant in-process production steps, as well as at the completion of final production and release activities.

FDA-483 #7

The letter describes a global initiative to assess all aspects of your quality policies, processes and systems. This is an acceptable response to this FDA-483 observation.

July 26, 2004 Meeting

We acknowledge the responses you made during the meeting held on July 26, 2004 in the Detroit District office, and your firm's commitment to take whatever measures are necessary to bring your firm into compliance.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The violations noted during these inspections appear to be symptomatic of serious underlying problems at your firm. We expect you to initiate prompt and permanent corrective actions and to assure that your firm is in compliance with laws and regulations enforced by the FDA.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket approval applications for devices to which the Quality System regulation deficiencies are reasonably related will be approved until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties.

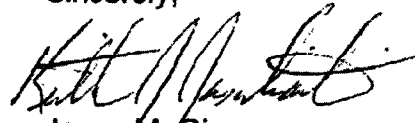
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Roche Diagnostics Corporation
Indianapolis, IN

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Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and to assure that your firm is in substantial compliance, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be directed to Melvin O. Robinson, Compliance Officer, Food and Drug Administration, at the above address.

Sincerely,



Joann M. Givens
District Director
Detroit District

for

Enclosed: FDA-483

cc:
Mr. Heino von Prondzynski
Head of the Diagnostics Division
F. Hoffmann-La Roche Ltd.
CH-4070 Basel
Switzerland